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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,770	05/31/2001	Richard E. Jones	018240-037	6457

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EXAMINER	
MCINTOSH III, TRAVISS C	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/867,770	JONES, RICHARD E.	
	Examiner	Art Unit	
	Traviss C McIntosh	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Amendment filed December 31, 2002 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claim 7 has been amended.

Remarks drawn to rejections of Office Action mailed October 1, 2002 include:

112 1st and 2nd paragraph rejections have been overcome by applicants' arguments and amendments and have been withdrawn.

103(a) rejection which has been maintained for reasons of record.

An action on the merits of claims 1-8 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

The rejection of claims 1-8 under 35 U.S.C. 103(a) as being unpatentable over McCarthy et al. (US Patent 5,378,693) in view of the combination of Huber et al. (US Patent 4,180,559) and of Ohno et al. (US Patent 4,017,647) is maintained for reasons of record.

The claims of the instant invention are drawn to an orally deliverable composition of 2'-deoxy-2'-(fluoromethylene)cytidine (FMdC) (0.5-50% weight of composition) for treating a neoplastic or viral disease wherein the encapsulation material is dissolution resistant at a pH of about 4-5 or less and will readily dissolve at a pH of about 4-5 or more. The composition may

further comprise an excipient and the encapsulation material may be cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, poly(vinyl acetate phthalate), hydroxypropyl methylcellulose acetate succinates, and cellulose acetate phthalate/diethylphthalate. Additionally, the encapsulation material may be copolymers of methacrylic acid and acrylic acid esters, or copolymers of methacrylic acid and methacrylic acid esters. The excipient (about 50-99.5% weight of composition) may be the encapsulation material, or there may be an additional excipient in the composition. The claims of the instant application are additionally drawn to a method for enhancing the oral bioavailability of a compound (FMdC) by administering a composition which comprises a compound encapsulated in a material which is dissolution resistant at a pH of 4 to 5 and readily dissolves in a pH of greater than about 4 to 5 to a mammal, wherein the process steps of the coating requirements weigh heavier than the compound which is coated.

McCarthy et al. disclose a composition which can be used to provide treatment of a patient afflicted with a carcinoma comprising administering the compound of formula (1), (1a), or (1b) (column 23, lines 35-43). Formula 1 of McCarthy et al. (see column 1) comprises FMdC wherein X_1 is hydrogen, X_2 is a halogen (fluorine), V is oxy, and B is radical on far right comprising Y_4 (hydrogen) and Y_5 (amino) (column 1, lines 20-50). The compound of McCarthy et al. is effective in slowing, interrupting, arresting, or stopping the growth of the carcinoma in the patient. The compound of McCarthy et al. is taught to be administered in any form or mode which makes the compound bioavailable in effective amounts, including and preferably orally. McCarthy et al. note that one skilled in the art of preparing formulations can readily select the proper form and mode of administration depending on the particular characteristics of the

compound selected, the disease state of the patient to be treated, the stage of the disease, and other relevant circumstances (column 24, lines 13-27). The compound of McCarthy et al. can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable excipients, wherein the proportion and nature are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. (column 24, lines 28-34). Suitable carriers or excipients to be used for the composition of McCarthy et al. are well known in the art wherein the compositions may be adapted for oral or parenteral use and may be administered in the form of tablets, capsules, suppositories, solution, suspensions, or the like (column 24, lines 1-6). For the purpose of oral therapeutic administration, the compound may be incorporated with excipients and include at least 4% of the active agent, and more particularly from between 4% - 70% (column 25, lines 10-19). The excipients taught by McCarthy et al. include starch or lactose, and disintegrating agents such as alginic acid, Primogel, and corn starch (column 25, lines 25-30). Other dosage unit forms may contain various materials which modify the physical form of the dosage unit, for example, as coatings of sugar, shellac, or other enteric coating agents (column 25, lines 37-41). What is not taught by McCarthy et al. is to use the specific encapsulation materials, such as hydroxypropyl methylcellulose phthalate as the enteric coating.

Ohno et al. teach to provide an improved method for providing enteric coatings on solid pharmaceutical dosage forms wherein the enteric coatings are soluble in the small-intestinal juice having a pH in the range of 4-8 (column 1, lines 35-66). Illustrative of the polymeric substances are (1) partial esters of at least one cellulose derivative having one or more substitution groups, such as, an alkyl cellulose (for example, methyl cellulose or ethyl cellulose), a hydroxyalkyl

cellulose (for example, hydroxyethyl cellulose or hydroxypropyl cellulose), a hydroxyalkyl alkyl cellulose (for example, hydroxyethyl methyl cellulose, hydroxyethyl ethyl cellulose, or hydroxypropyl methyl cellulose), or cellulose esters (for example, cellulose acetate and cellulose acetate butyrate partially retaining hydroxyl groups of cellulose), with at least one polybasic acid, such as, succinic acid, maleic acid, phthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, trimellitic acid, or pyromellitic acid; (2) partial esters of at least one vinyl polymer or copolymer containing in its molecules vinyl alcohol units (for example, partially saponified polyvinyl acetate or polyvinyl acetoacetal) with at least one of the above-mentioned polybasic acids; (3) polymers of polymerizable monomers having carboxyl groups, such as, acrylic acid or methacrylic acid, or copolymers involving such a monomer unit; (4) polymeric substances convertible into the acid form by hydrolysis, such as, the polymers or copolymers of acrylic or methacrylic esters; and (5) polymers or copolymers prepared from monomers having carboxyl groups in the salt form, such as, sodium acrylate which are sodium methacrylate and readily convertible into the acid form (column 1, line 67 – column 2, line 27).

Huber et al. disclose the use of hydroxypropyl methylcellulose phthalate to protect an active agent from acid degradation in the stomach, allowing the agent to be dissolved at the pH of 5.0 to 5.5, in order to permit dissolution and absorption of the drug substance (column 2, lines 35-42) by releasing the active compound under the slightly acidic conditions of the duodenum, where the compound is available for absorption into the bloodstream (column 2, line 62 – column 3, line 2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the protective agent of Ohno et al. and Huber et al. in combination with the

compositions of McCarthy et al. because it is known that the acidic conditions in the stomach degrade compounds thereby prohibiting compounds from being absorbed by the bloodstream and in turn prohibiting the compounds from working as needed. One with ordinary skill would be motivated to use these enteric coatings as it is noted by Huber et al. that the concept of using enteric coatings to protect drugs that are destroyed in gastric fluids is, of course, well known (column 2, lines 6-8), and McCarthy et al. specifically teach that other enteric coating agents can be used (column 25, lines 40-41) to protect the compound from degradation.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, McCarthy et al. does contemplate the use of **other enteric coatings** (column 25, lines 40-41) and that in determining the effective dose a number of factors are considered by the attending diagnostician, including but not limited to: species of the mammal: its size, age, and general health; the specific disease involved; the degree of or involvement or severity of the disease; the response of the individual patient; the particular compound administered; the mode of administration; **the bioavailability characteristics of the preparation administered**; the dose regimen selected; the use of concomitant medication; and other relevant circumstances (column 23, line 64 – column 24, line 6). As applicant attests to in the response filed in page 3 of remarks, these enteric coatings were known in the art before the present specification was filed

and were known to possess common attributes or features, that is the dissolution profile which has a direct correlation to the bioavailability.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant's argument is not convincing on its face. The compound FMdC is known in the art to be encapsulated, and the encapsulation material is known in the art to provide increased bioavailability to solid dosage forms. The art of record does contemplate the use of various enteric coatings on a composition of FMdC based on the bioavailability of the preparation, and the various enteric coatings claimed in the instant application are disclosed completely in the art of record as means for providing an acceptable dissolution profile.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss C McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
March 17, 2003